



72. (New) The composition according to Claim 65 wherein L is a ligand of formula (i).

73. (New) The composition according to Claim 65 wherein one L is a ligand of formula (i) and one L is a ligand of formula (v).

### **R E M A R K S**

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining in this application be allowed.

#### **Amendments**

Claims 52 and 61 were amended to recite the linker definition previously found in Claims 55 and 64. In view of these amendments, Claims 55 and 64 were canceled without prejudice or disclaimer and Claims 56 and 65 amended to correct claim dependency. Claims 58, 59, and 67 were amended to utilize the newly introduced ligand formulas in place of repeating the structures.

Claims 52 and 61 were further amended to delete reference to the benzimidazole and the 4-(3-nitrophenyl)-1,4-dihdropyridine ligands from the Markush group of ligands.

New Claims 69-73 have been added. Support for new Claim 69 is found in Applicants' specification at least in compound 79 of Fig. 10. Support for Claims 70 and 72 is found at least in compounds 1-36 of the table entitled "Multibinding Calcium Channel Antagonist Table" following Fig. 21. Support for Claims 70 and 72 is found at least in compounds 603-629 of the table.

No new matter has been added.

These amendments have been made in accordance with 37 C.F.R. §1.121 as amended on November 7, 2000. As required, attached hereto is an appendix illustrating the changes made to Claims 52, 56, 58, 59, 61, 65, and 67.

Entry of these amendments is earnestly solicited.

In view of these amendments, Claims 52-54, 56, 58-63, 65, and 67-73 are now presented for continued examination.

Information Disclosure Statement

As noted in the Office Action, the Information Disclosure Statement filed December 29, 2000 included a request to consider two copending applications: U.S. Serial No. 09/493,081 and U.S. Serial No. 09/674,422. Both of these applications have now been abandoned and copies of the Express Abandonments filed with the United States Patent and Trademark Office are enclosed. Accordingly, Applicants' previous request to consider copending applications is now moot.

Denial of Priority Claim

Applicants note that the Office Action repeats the assertion denying Applicants claim to priority to U.S. Provisional Patent Application Serial No. 60/088,465 and 60/093,068. In view of this denial, Applicants herewith withdraw their claim of priority to these applications and, accordingly, have amended the specification to delete reference to these applications.

Provisional Obviousness Type Double Patenting Rejection

Claims 52-58 and 61-67 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting over Claims 39-52 of U.S. Patent Application Serial No. 09/493,081. Applicants note that this rejection has been obviated by abandonment of the '081 application. Withdrawal of this provisional rejection is requested.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 52-54 and 61-63 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed. Specifically, this rejection is directed to the assertion in the Office Action that the failure of these claims to define the linker allows for a virtually unlimited number of compounds to fall within the scope of the claimed genus.

Applicants do not acquiesce in this rejection. However, in order to expedite what is believed to be allowable, Claims 52 and 61 have been amended to insert the recitation for the linker group found in previously presented and non-rejected Claims 56 and 65 respectively. By virtue of these amendments, this rejection is now moot. Withdrawal of this rejection is earnestly solicited.

Claims 52-57 and 61-66 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while enabling for specific ligands known to bind to calcium channels, allegedly does not reasonably provide enablement for compounds of the formula  $(L)_p(X)_q$  utilizing the benzimidazole ligand alone. Moreover, the homomeric benzimidazole dimers were allegedly known in the art and the specification did not show how to use such homomeric compounds for binding to a  $Ca^{++}$  channel. For the following reasons, this rejection is obviated-in-part and is traversed-in-part.

This rejection is obviated-in-part to the extent that the ligands recited in the Markush group of Claims 52 and 61 no longer include the benzimidazole group and, accordingly, homomeric benzimidazole dimers are not within the scope of the claimed invention.

This rejection is traversed-in-part to the extent that the cited prior art does not read on such homomeric compounds. Specifically, the cited art is directed to dimeric benzimidazole compounds linked through either a butyl or propyl group. However, even if a homomeric

compound prepared from the benzimidazolyl ligand depicted in previously presented Claim 52 was employed, this compound would necessarily be different from the structures of the cited Van Albada abstract because the previously claimed structure necessarily would have at least 6 carbon atoms and a linker group between the two benzimidazole rings; neither of which are disclosed by Van Albada.

In view of the above, withdrawal of this rejection is requested.

**Rejections Under 35 U.S.C. §112, second paragraph**

Claims 52-54 and 61-63 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly omitting essential structural elements of the claimed invention.

Applicants do not acquiesce in this rejection. However, in order to expedite what is believed to be allowable, Claims 52 and 61 have been amended to insert the recitation for the linker group found in previously presented and non-rejected Claims 56 and 65 respectively. By virtue of these amendments, this rejection is now moot. Withdrawal of this rejection is earnestly solicited.

**Rejection Under 35 U.S.C. §102(e)**

Claims 52-68 stand provisionally rejected under 35 U.S.C. §102(e) as being anticipated by copending Application No. 09/493,081. Applicants note that this rejection has been obviated by abandonment of the '081 application. Withdrawal of this provisional rejection is requested.

**Rejection of Claims 52-57 and 61-66 under 35 U.S.C. §102(b)**

Claims 52-57 and 61-66 stand rejected under 35 U.S.C. §102(b) over Branca, et al., U.S. Patent No. 4,808,605 which allegedly discloses compounds made up of two distinct portions; one containing a benzimidazole group and the other a bicyclic group.

Without acquiescing in this rejection, Applicants submit that it has been obviated in view of the amendments to Claims 52 and 61 which deleted the benzimidazolyl ligand from the Markush group of suitable ligands. Withdrawal of this rejection is earnestly solicited.

Rejection of Claims 52-56, 58, 61-65 and 67 under 35 U.S.C. §103(a)

Claims 52-56, 58, 61-65 and 67 stand rejected under 35 U.S.C. §103(a) over Joslyn, et al., J. Med. Chem., 1988) which allegedly discloses dimeric 4-(3-nitrophenyl)-1,4-dihydropyridine compounds.

Without acquiescing in this rejection, Applicants submit that it has been obviated in view of the amendments to Claims 52 and 61 which deleted the 4-(3-nitrophenyl)-1,4-dihydropyridine ligands from the Markush group of suitable ligands. Moreover, the dimeric 4-(2-chlorophenyl)-1,4-dihydropyridine compounds retained within the claimed invention are structural distinguished over Joslyn both on the substituent recited on the phenyl moiety (2-chlorophenyl versus 3-nitrophenyl) and on the point of attachment to the linker. In view of the above, Applicants maintain that this rejection is now moot.

Withdrawal of this rejection is earnestly solicited.

Inventorship

In addition, the undersigned has reviewed the inventorship of the now claimed invention and has determined that while Burton G. Christensen was correctly named as an inventor of the present application at the time it was filed, Dr. Christensen is not an inventor of the claims now presented in the application. The remaining inventors Yu-Hua Ji, Maya Natarajan, John Griffin, and Thomas E. Jenkins are correctly named. Accordingly, a petition under 37 C.F. R. §1.48(b) to correct the inventorship is enclosed herewith.

The undersigned further notes for the record that the related applications U.S. Serial No. 09/493,081 and U.S. Serial No. 09/674,422, which named Yu-Hua Ji, Maya Natarajan, and

John Griffin as inventors, incorrectly omitted Thomas Jenkins and Burton Christensen. However, as the '081 and '422 applications have been expressly abandoned, their inventorship is now moot.

**CONCLUSION**

In view of the above, Applicants respectfully submit that this application, in which Claims 52-54, 56, 58-63, 65, and 67-73 are pending, is now in condition for allowance. A notice to that effect is earnestly solicited.

Should the Examiner wish to discuss any aspect of the application, the Examiner is invited to telephone the undersigned or Jeffrey Hagenah.

Respectfully submitted,

Date: October 4, 2001

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**VERSION OF SPECIFICATION WITH MARKINGS TO SHOW CHANGES MADE**

Page 1, lines 3-7

Continuing Application Data

This application is a continuation-in-part of U. S. Application Serial No. 09/325,557, filed June 4, 1999, now abandoned, which, [is a continuation of U.S. Applications Serial No. 60/088,465 (June 8, 1998), Serial No. 60/093,068 (July 16, 1998) and U.S.] in turn, claims the benefit of U.S. Provisional Application Serial No. 60/103,866, filed [() October 12, 1998]].

**VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE**

52. (Amended) A compound represented by Formula I:



where

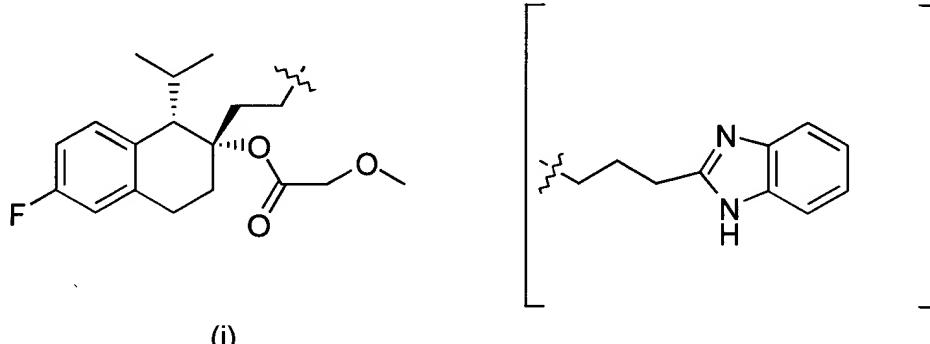
each L is a ligand that may be the same or different at each occurrence;

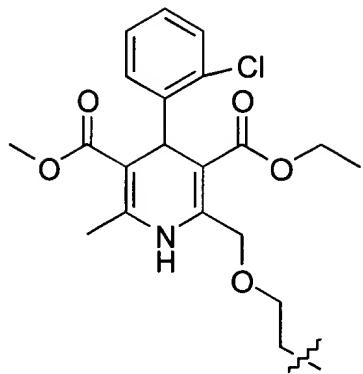
X is a linker that may be the same or different at each occurrence;

p is an integer of from 2 to 10;

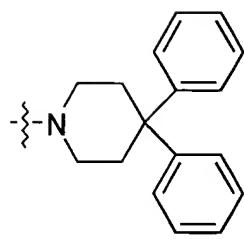
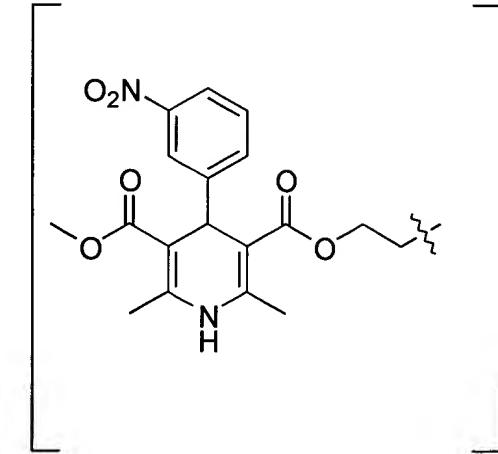
q is an integer of from 1 to 20;

and wherein L is selected from the group consisting of [the following ligands] formula (i), formula (ii), formula (iii), formula (iv), formula (v), and formula (vi):

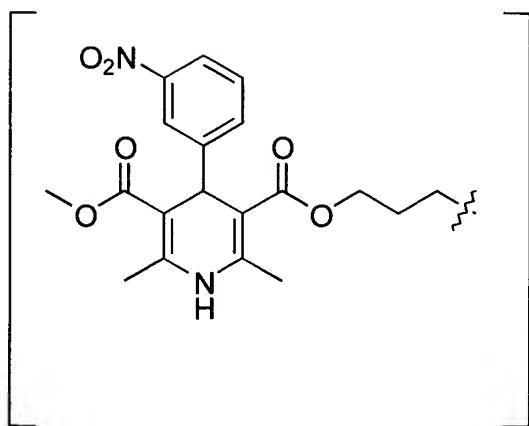


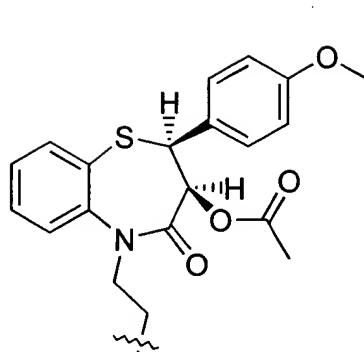


(ii)

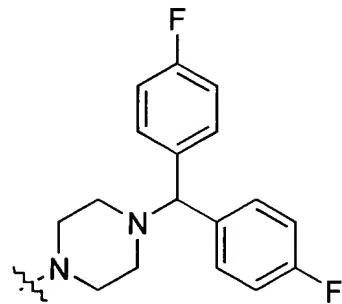


(iii)

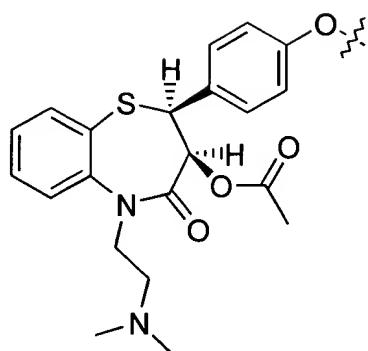




(iv)

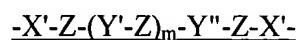


(v)



(vi)

and wherein each linker X<sub>n</sub> is represented by the following formula:



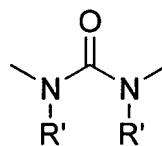
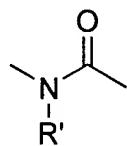
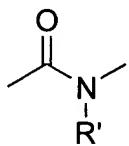
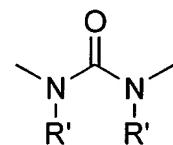
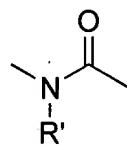
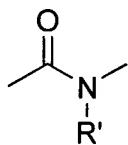
in which:

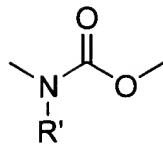
m is an integer from 0 to 20;

X' at each separate occurrence is -O-, -S-, -S(O)-, -S(O)2-, -NR-, -NRR', -C(O)-, -C(O)O-, -C(O)NH-, -C(S)-, -C(S)O-, -C(S)NH- or a covalent bond, where R and R' at each separate occurrence are as defined below for R' and R":

Z is at each separate occurrence selected from alkylene, substituted alkylene, alkylalkoxy, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, substituted arylene, heteroarylene, heterocyclene, substituted heterocyclene, crown compounds or a covalent bond;

Y' and Y" at each separate occurrence are selected from -S-S-, a covalent bond or a structure selected from the following group:





-S(O)<sub>n</sub>-CR'R''-

-S(O)<sub>n</sub>-NR'-

in which:

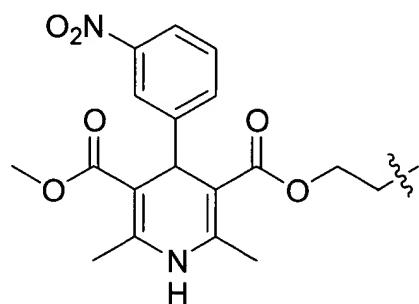
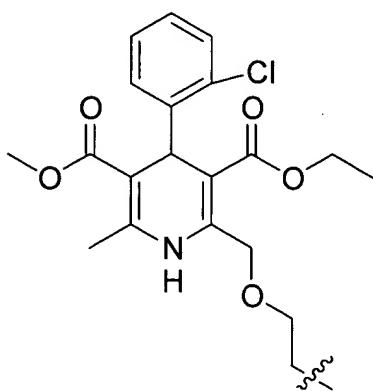
n is 0, 1 or 2; and

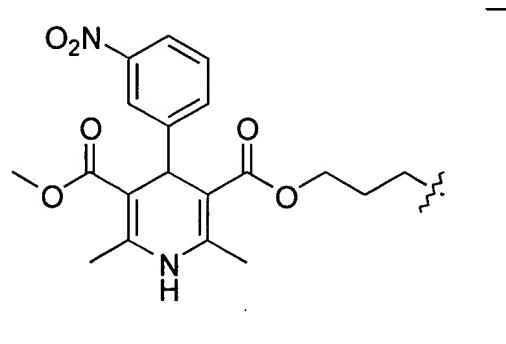
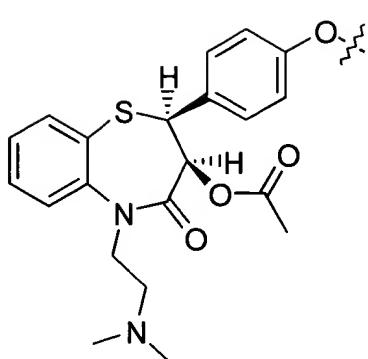
R' and R'' at each separate occurrence are selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl or heterocyclic;

and further wherein each of said ligands comprises a ligand domain capable of binding to a Ca<sup>++</sup> channel.

56. (Amended) The compound according to Claim [55] 52, wherein p is 2 and q is 1.

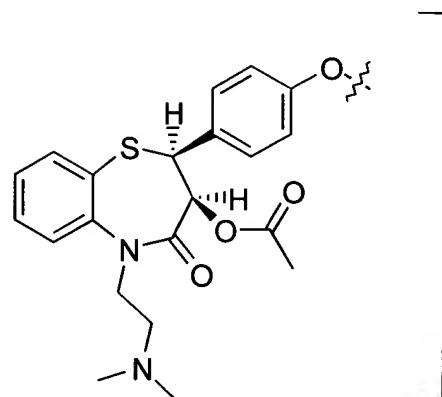
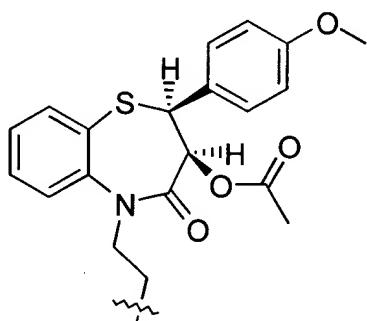
58. (Amended) The compound according to Claim 56, wherein L is [selected from the group consisting of the following ligands:





a ligand of formula (ii) or of formula (vi).

59. (Amended) The compound according to Claim [57] 56, wherein L is [selected from the group consisting of the following ligands:



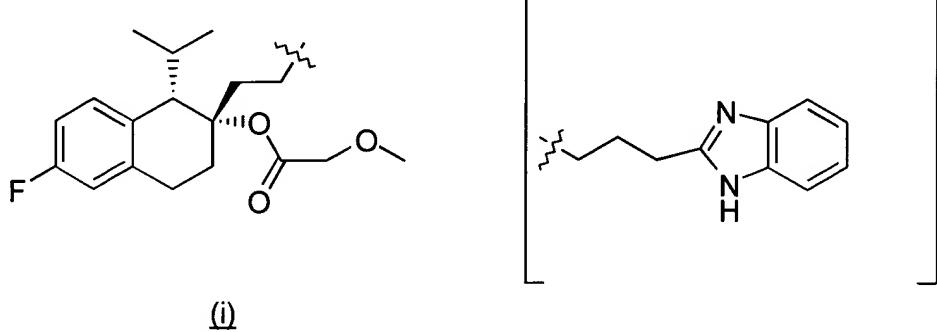
a ligand of formula (iv) or of formula (vi).

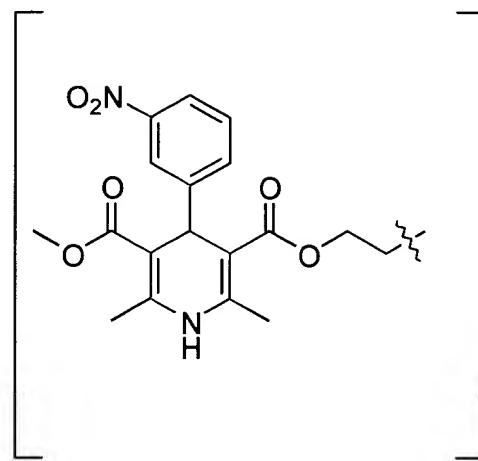
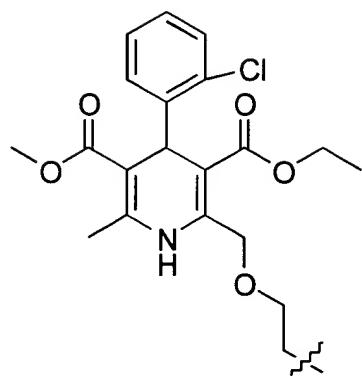
61. (Amended) A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of one or more compounds represented by Formula I:



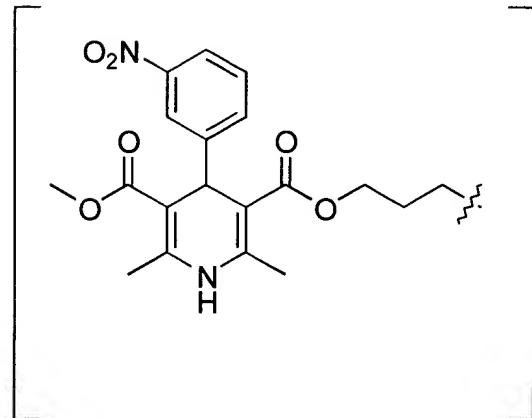
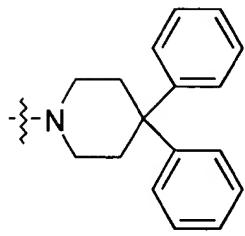
where

each L is a ligand that may be the same or different at each occurrence;  
X is a linker that may be the same or different at each occurrence;  
p is an integer of from 2 to 10;  
q is an integer of from 1 to 20;  
and wherein L is selected from the group consisting of [the following ligands] formula (i), formula (ii), formula (iii), formula (iv), formula (v), and formula (vi):

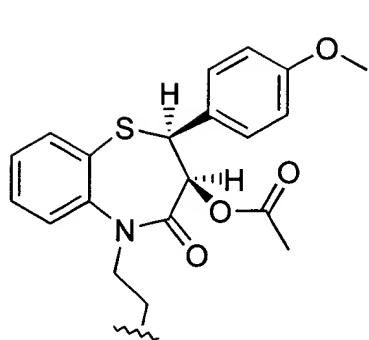




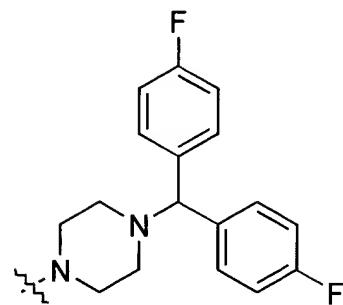
(ii)



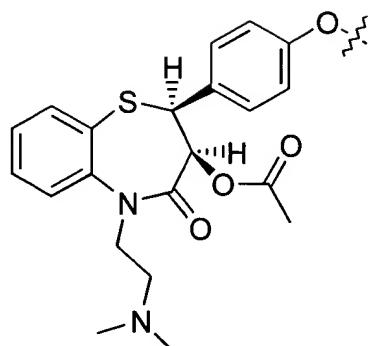
(iii)



(iv)



(v)



(vi)

and wherein each linker X<sub>n</sub> is represented by the following formula:

-X'-Z-(Y'-Z)<sub>m</sub>-Y"-Z-X'-

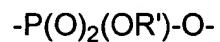
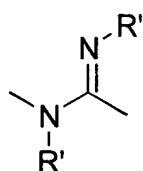
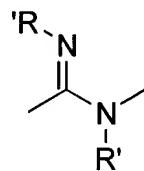
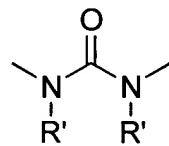
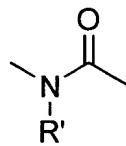
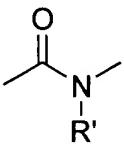
in which:

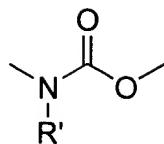
m is an integer from 0 to 20;

X' at each separate occurrence is -O-, -S-, -S(O)-, -S(O)2-, -NR-, -NRR', -C(O)-, -C(O)O-, -C(O)NH-, -C(S)-, -C(S)O-, -C(S)NH- or a covalent bond, where R and R' at each separate occurrence are as defined below for R' and R":

Z is at each separate occurrence selected from alkylene, substituted alkylene, alkylalkoxy, cycloalkylene, substituted cycloalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, substituted arylene, heteroarylene, heterocyclene, substituted heterocyclene, crown compounds or a covalent bond;

Y' and Y" at each separate occurrence are selected from -S-S-, a covalent bond or a structure selected from the following group:





-S(O)<sub>n</sub>-CR'R''-

-S(O)<sub>n</sub>-NR'-

in which:

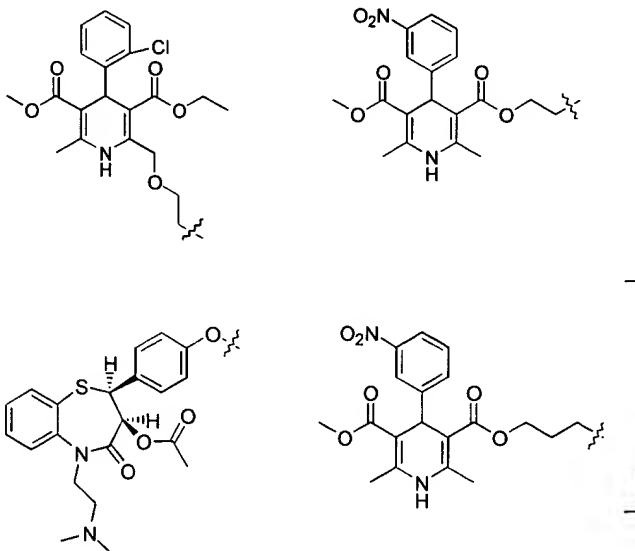
n is 0, 1 or 2; and

R' and R" at each separate occurrence are selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl or heterocyclic;

and further wherein each of said ligands comprises a ligand domain capable of binding to a Ca<sup>++</sup> channel.

65. (Amended) The composition according to Claim [64] 61, wherein p is 2 and q is 1.

67. (Amended) The composition according to Claim 65, wherein L is [selected from the group consisting of the following ligands:



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Application No. 09/456,429  
Attorney's Docket No. 032367-451 (AMI-015-RP1)  
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a ligand of formula (ii) or of formula (iv).